REMARKS

Claims 1-17, 24, 26-28 and 31 were pending for prosecution in this Application while claims 18-23, 25, 29 and 30 have been withdrawn. Claims 1-17, 24, 26-28 and 31 are now cancelled and replaced with new claims 32-47. No new matter is believed to have been introduced. The new claims address the concerns of the Examiner laid out on pages 3-5 of the office action dated February 11, 2009 and more distinctly point out the invention. Examples of support for the claims provided in the specification may be found for example on pages 15-17 and 19-20 including descriptions of modifications and proteins that fall within the 35% sequence identity demonstrating that that this set of proteins has a relatively small number of species. Support for claims 37 and 39 can be found on page 19 lines 6-14.

The Examiner is thanked for pointing out the discrepancies between the sequence listing and several of the figures. The sequence listing has been amended to correct a typographical error (the omission of a "c" for formerly identified SEQ ID NO:21, now SEQ ID NO:20, in Figure 11C) and to delete duplicate sequences. The amended sequence listing is being filed with this response. The Applicants have amended Figures 11C, 13, 14-2 and 14-3 to correct inconsistencies between the sequence identifiers in the figures and the sequence listing. Applicants believe that no new matter has been introduced.

Applicants request that the replacement drawings and the corrected sequence listing be entered. Applicants have included an annotated copy of the amendments to the drawings.

The Examiner has rejected the claims under 35 U.S.C. §112 as lacking written description and enablement and under 35USC §102 and 35 U.S.C. §103 citing Beck et al.

Rejection under 35 U.S.C. §112 First Paragraph

Written description

A representative number of species for the genus of proteins is required. The Examiner states that only two species are described. In fact, 24 mutants are described. (See page 18 of the Application.)

Applicants have described specifically at least 9 species of the claimed genus of proteins. These are listed for example on page 5 and are PA/A, PA/AA, PA/PGA, PA/PAPA, Δ PA, PA/K, PA/G, PA/D and PA/P. These are also described on page 17, line 32 of the Application. The Applicants actually generated 24 β-bridge site mutants (Application page 18, line 16) which were purified and characterized according to the description in Example 1 using MBP conjugates.

Example 1 describes how oligonucleotide mixtures can be used to generate desired mutants (page 25). Methods are also presented for creating mutants by creating a T7 Endo I mutant in which the entire β-bridge is deleted and then adding back synthetic oligonucleotides having the desired sequence. Accordingly, dipeptide PA was replaced by single amino acids, dipeptides and tetrapeptide to generate a large number of mutants with examples including ME(PA/G), ME (PA/AA), ME(PA/PGA) and ME(PA/PAPA). (Application page 28)

Assays were described for analyzing the activities of the mutants in for example, Example 2. These detailed descriptions cover all the claimed functionalities. The assays were illustrated for two mutants but a person of ordinary skill in the art would readily understand that these assays were not specific for the exemplified mutants but could be applied to any of the mutants made according to Example 1.

When there is substantial variation within a genus, a sufficient variety of species should be provided to reflect variation within the genus. In this case, there is a limited amount of variation of species and numerous examples are provide.

Applicants have specified that the claimed composition varies from T7 Endo I by an amino acid change in the β bridge which is a 6 amino acid region in SEQ ID NO:12 corresponding to amino acid residues 44-49 (Val, Ile, Pro, Ala, Ser, and Asn). This bridge is a small and highly specific region of a protein with 145 amino acids. The 24 examples of variants with the desired properties in this region is a sufficient description of a representative number of species. The corresponding β-bridge in other species in the genus can be readily recognized as described below.

Characteristics of a protein are provided that correlate structure with function.

The structure of T7 Endo I has been well studied and is illustrated in Figure 12 of the application. Those proteins which are identified by a BLAST search in the Application (Figure 14) as having at least 35% amino acid identity can be threaded through the T7 Endo

I structure with a very close match (see examples of threaded molecules attached as Appendix 1). This is readily done using the Conserved Domain Architecture Retrieval Tool to identify members of the claimed class from their amino acid sequences (Application page 15). The catalytic regions are clearly identifiable and so is the β-sheet bridge (β-bridge) which "forms part of an extended and tightly associated anti-parallel β-sheet" (application page 1) and which is the target of the claimed amino acid alterations.

For the above reasons, the present claims not only provide a representative number of species by actual reduction to practice but also disclose relevant identifying characteristics in the form of structure. Thus, the present claims meet the requirements of the test laid out in *University of California v. Eli Lilly & Co.*, 43 USPQ 2d 1938.

The Examiner is therefore respectfully requested to reverse the rejection.

Enablement

The present claims are enabled under 35 U.S.C. §112 under the *In re Wands* factors.

In re Wands presents eight factors for determining undue experimentation:

(i) Quantity of experimentation necessary;
(ii) Amount of direction or guidance presented;
(iii) Presence or absence of working examples;
(iv) The nature of the invention;
(v) The state of the prior art;

(vi) The relative skill of those in the art;

(vii) The predictability of the art; and

(viii) The breadth of claims.

As discussed above, the present Application describes in detail with working examples (Examples 1 and 2) how to make mutants, where to make mutants, and how to assay the mutants for desirable properties. With this description, only very routine experimentation would be required to practice the scope of the claimed invention. The structure of the T7 Endo I has been well described in the prior art. Unfortunately, it is toxic and therefore has not been made successfully in recombinant form. Applicants first discovered a mutant that had altered properties and then on further investigation determined that this effect was not specific for a particular mutant but instead was a general effect arising from a change of at least one amino acid in the amino acid sequence of the β-bridge of SEQ ID NO:12 resulting in reduced toxicity and the additional properties as specified.

Creating mutants in proteins is well established in the art such that a person of ordinary skill in molecular biology should be able to follow the instructions provided in the examples of the present Application. Applicants have shown by analyzing more than 20 mutants that a mutation in the β-bridge of a protein having at least 35% sequence identity with SEQ ID NO:12 which also has two catalytic domains separated by a β-bridge predictably gives rise to a reduction in toxicity.

Applicants assert that the amended claims distinctly describe an invention that is fully enabled and request that the Examiner reverse the rejection.

The Examiner has cited Witkowski et al. and Branden et al. to illustrate the assertion that a modification in the sequence of a catalytic domain may have unpredictable consequences on enzyme activity. These references however are not relevant to the present claimed invention which is focused on the changes outside the catalytic domain in a very specific short stretch of amino acids with a clearly defined structure.

Rejection of claims based on non-enabled prior art

Rejection under 35 U.S.C. §102

A reference should be enabled for the claimed invention for it to be considered anticipatory under 35 U.S.C. §102. By the same criteria of enablement used by the Examiner above, the Applicants respectfully assert that the prior art is not enabled and therefore not valid prior art.

The Examiner has rejected claims 1, 13, 14, 15 and 17 as anticipated by the Beck et al. reference, which describes a sequence of the entire T3 genome. Table 5 in the publication lists sequence similarities between T3 positions, and corresponding T7 positions but does not match these similarities with any particular genes. Moreover, Beck et al. do not suggest creating a recombinant protein with the claimed characteristics. It would not be possible to deduce the claimed invention without undue experimentation particular in the absence of such a suggestion. Moreover, the related wild type T7 Endo I is toxic to the host cell. This is a significant barrier to creating the recombinant protein.

However, a reference must be enabled in order to be novelty-destroying. Because Beck et al. neither disclose a recombinant protein nor does the reference enable a person of ordinary skill in the art to make the claimed composition, the rejection under 35 U.S.C. §102 should be reversed.

Rejection under 35 U.S.C. §103

The Examiner has rejected claims 24 and 31 as unpatentable over Beck et al. Claim 24 now corresponds to claim 44. Claim 31 has been deleted.

The claimed composition differs from wild type T7 Endo I and as such the claimed characteristics could not be predicted from a genomic sequence of a different phage (T3).

The Applicants respecfully request that the rejection under 35 U.S.C. §103 be reversed.

CONCLUSION

Applicants respectfully submit that this case is in condition for immediate allowance. Early and favorable consideration leading to prompt issuance of this Application is earnestly solicited.

Applicants petition for a two-month extension of time and authorize that the extension fee of $245 be charged to Deposit Account No. 14-0740. Applicants authorize that any deficiencies that may be due be charged to the same Account.

Respectfully submitted,

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